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Application No.	:	**2,394,717**
Owner	:	GWATHMEY, JUDITH K.
Title	:	**IRON CHELATOR DELIVERY SYSTEM**
Classification	:	A61K-9/127
Your File No.	:	**PAT 52615W-1**
Examiner	:	Wesley Sharman

YOU ARE HEREBY NOTIFIED OF :

- A REQUISITION BY THE EXAMINER IN ACCORDANCE WITH SUBSECTION 30(2) OF THE *PATENT RULES*;
- A REQUISITION BY THE EXAMINER IN ACCORDANCE WITH SECTION 29 OF THE *PATENT RULES*.

IN ORDER TO AVOID **MULTIPLE ABANDONMENTS** UNDER PARAGRAPH 73(1)(A) OF THE *PATENT ACT*, A WRITTEN REPLY **TO EACH REQUISITION** MUST BE RECEIVED WITHIN 6 MONTHS AFTER THE ABOVE DATE.

The number of claims in this application is 38.

Applicant's letter of November 5, 2004 has been received and the application has been examined having regard to applicant's arguments and amendments. However, the examiner considers that the application does not comply with the *Patent Act* or *Rules* in respect of the defects noted below.

A search of the prior art has revealed the following:

References Re-Applied:

Publication		
Lau et al.	J. Lab. Clin. Med.	1983, 101, 806-816
Lau et al.	Brit. J. Haemato.	1981, 47, 505-518
Young et al.	Brit. J. Haemato.	1979, 41, 357-363
Rahman	Dev. Iron Chelators Clin. Use Proc. Symp. 2nd	1981, 211-225
Hopkins	Drugs of the Future	1979, 4(7), 500-506
Rahman et al.	Liposomes Immunobiol. Proc. Natl. Symp.	1980, 285-299
Leserman et al.	Nature	1980, 288, 602-604

European Patent Office Application

0068314	Jan. 5, 1983	Blake

Canadian Patent Document

2084187	Jan 23, 1991	Rudolf et al.

Reference Applied:

Publication		
Klibanov et al.	Am. J. Physiol.	1991, 261, 60-65
Torchilin et al.	Biochem. Biophys. Res. Commun.	1979, 89(4), 1114-1119
Dufresne et al.	Biochim. Biophys. Acta	1999, 1421(2), 284-294
Maruyama et al.	Proc. Natl. Acad. Sci. USA	1990, 87, 5744-5748
Maruyama et al.	Adv. Drug. Deliv. Rev.	1999, 40(1-2), 89-102
Vingerhoeds et al.	Immunomethods	1994, 4(3), 259-272

Lau et al. (1983) disclose liposomes comprising iron chelators and their use in treating transfusional iron overload.

Lau et al. (1981) disclose liposome-encapsulated desferrioxamine and its use in treating iron overload.

Young et al. disclose liposome-entrapped desferrioxamine and its use as a novel approach to iron chelation therapy.

Rahman discloses liposomes as delivery systems for iron chelators.

Hopkins discloses liposome-entrapped desferrioxamine.

Rahman et al. disclose application of liposomes in metal chelation therapy.

Leserman et al. disclose targeting to cells of fluorescent liposomes covalently coupled with monoclonal antibodies or protein A.

Blake discloses liposomal formulations of desferrioxamine for treating rheumatoid arthritic diseases.

Rudolf et al. disclose ^{99m}Tc-labelled liposomes.

Klibanov et al. disclose the coupling of myosin heavy chain to liposomes.

Torchilin et al. discloses liposomes covalently coupled to antimyosin antibodies.

Dufresne et al. disclose the targeting of lymph nodes with liposomes bearing anti-HLA-SDR Fab' fragments.

Maruyama et al. (1990) disclose immunoliposomes bearing the monoclonal IgG antibody 34A and the use of these immunoliposomes for targeting pulmonary endothelial cells.

Maruyama et al. (1999) discloses the targeting of tumors using liposomes covalently linked to antibodies.

Vingerhoeds et al. review the attachment of antibodies to the surface of liposomes to confer specificity for certain cell or organs expressing the targeted antigenic determinant.

The examiner has identified the following defects in the application:

Claims 13, 15, 18-23, 26-29, and 31-35 do not comply with paragraph 28.2(1)(*b*) of the *Patent Act*. Lau et al. (1981), Rahman and Rahman et al. all disclosed the claimed subject matter before the claim date. The applicant argued in the correspondence dated November 5, 2004 that Rahman fails to disclose a targeting agent that can provide specificity to an iron chelator delivery system. The examiner respectfully disagrees. Rahman explicitly discloses the use of galactolipids such as galactocerebroside as a targeting agent and discloses that the existence of galactose receptors on the surface of liver parenchymal cells. In the abstract, Rahman states "by modifying the surface properties, suitable liposomes could be prepared to target the encapsulated iron chelators specifically to a desired organ". Hence, Rahman does disclose liver-targeted iron chelator delivery systems that fall within the scope of claims 18-23, 26-29 and 31-35. In addition, the method used by Rahman to prepare the liver-targeted iron chelator delivery systems falls within the scope of the general method defined in claims 13 and 15. The applicant's argument that Lau et al. and Rahman et al. indicates that In at least certain applications, liposomes containing galactolipid are less effective at iron removal than those without galactolipid and that this teaches away from targeted iron chelator delivery systems is found unpersuasive. While Lau et al. and Rahman et al. do disclose that liposomes made with galactocerebroside is less effective for iron removal from mice given DRBC, they is more effective in removing iron from mice given ferritin. As such, these documents discloses that targeted iron chelator delivery systems are useful in the removal of iron from the liver and does not teach away from the use of targeted iron chelator delivery systems for iron removal. As such, the subject matter of claims 13, 15, 18-23, 26-29 and 31-35 was disclosed by these documents before the claim date.

Claims 1-6, 8-23 and 25-35 do not comply with section 28.3 of the *Patent Act*. The subject matter of these claims would have been obvious on the claim date to a person skilled in the art or science to which they pertain having regard to either document by Lau et al., Young et al., Rahman, Hopkins et al., Rahman et al. or Blake et al. in light of the teachings of any of Klibanov et al., Torchilin et al., Dufresne et al. or either document by Maruyama et al. All of Lau et al., Young et al., Rahman, Hopkins et al., Rahman et al. or Blake et al. disclose the use of liposomes encapsulating iron chelators for the treatment of iron overload. It states in the current specification on page 1, lines 4-8 that "Iron-overload due to transfusion currently occurs with any patient who receives more than 30 or 40 transfusions over the course of his or her life. The excess iron can injure any organ in the body. The heart and liver are particularly susceptible to damage and failure of one of these organs is often the cause of death in patients with transfusional iron-overload." In

light of this, it is obvious that improved treatment of iron overload could be achieved by specifically targeting the liposomes disclosed by Lau et al., Young et al., Rahman, Hopkins et al., Rahman et al. or Blake et al. to the heart or the liver. An obvious method for accomplishing specific targeting of these liposomes to the heart or the liver is attach targeting agent to heart or liver specific proteins and receptor. Klibanov et al., Torchilin et al., Dufresne et al., either document by Maruyama et al. and Vingerhoeds et al. all disclose the targeting of specific tissues using liposomes coupled to appropriate antibodies and are representative examples of the use of antibodies to target liposomes to specific cells or organs expressing the targeted antigenic determinant. In fact, Klibanov discloses liposomes coupled to antibodies to myosin heavy chain and the specific localization of these liposomes in the myocardium in rabbits while Torchilin discloses liposomes coupled to antimyosin antibodies and the preservation of antimyosin antibody activity after covalent coupling of the antibody to liposomes. Since the above documents indicate that it is well-known in the art to couple antibodies to liposomes in order to target specific cells or organs, it would have been obvious to a person skilled in the art to target the liposomes comprising an iron chelator as disclosed by either document by Lau et al., Young et al., Rahman, Hopkins et al., Rahman et al. or Blake et al. to the heart or to the liver by coupling these liposomes to antibodies specific for antigenic determinants expressed by cells in the heart or in the liver. In addition, it would have be obvious to a person skilled in the art to further tag these liposomes with a label that is used for diagnostic imaging in light of the disclosures by Leserman et al. or Rudolf et al.

The subject matter of claims 7, 23 and 36-38 as amended by applicant's correspondence dated November 5, 2004, does not comply with section 38.2 of the *Patent Act* because it is not reasonably to be inferred from the specification or drawings as originally filed. There is nothing in the original specification to suggest that the presence of cationic or anionic groups in the liposomes would result in site specific delivery of the liposomes to tissues needing treatment for iron-overload; particularly, the heart and the liver. As such, there is no support in the original description for the targeting agents being cationic or anionic groups. In addition, claims 7, 23 and 36-38 do not comply with section 84 of the *Patent Rules*. The description fails to provide a sound line of reasoning for cationic or anionic groups leading to the targeting of liposomes to tissues needing treatment for iron-overload, in particular, the heart and the liver. The factual support described in the example does not lead to the conclusion that the subject matter of these claims would have the predicted utility. (Apotex Inc. v. Wellcome Foundation Ltd., 2002 SCC 77). The doctrine of sound prediction in Canada has three components (Apotex Inc. v. Wellcome Foundation Ltd., 2002 SCC 77):

1) There must be a factual basis for the prediction.
2) The inventor must have, **at the claim date**, an articulable and sound line of reasoning from which the desired result can be inferred from the factual basis.
3) There must be a proper disclosure.

There is no factual basis in the original description for cationic or anionic charged groups could act as targeting agents for liposomes comprising an iron chelator and that the presence of charged groups would result in targeting of liposomes comprising an iron chelator to the heart, the liver or other tissue requiring treatment for iron-overload.

Claims 8 and 24 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. Endothelial cells are not cardiac proteins and therefore, the inclusion of endothelial cells in a Markush group defining cardiac proteins is inappropriate.

Claims 9 and 25 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. Defining that the lipid carrier is tagged is ambiguous. Tagging does not have a well-known meaning in the art and therefore, it is not evident what is meant by tagging the lipid carrier. In addition, claims 9 and 25 are broader in scope than the teaching of the description. To comply with section 84 of the *Patent Rules*, the claims must specify that the lipid carrier is tagged with a label that is used for diagnostic imaging (see page 5, line 2).

Claim 10 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. The term "the liver cell targeting agent" has no antecedent.

Claims 26 and 29 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. The use of the term "suitable" leads to a lack of clarity. It is not evident in what manner the delivery system is suitable for administration by injection into the venous circulation (claim 26) or for administration to the mammal (claim 29).

Claim 31 is broader in scope than the teaching of the description. To comply with section 84 of the *Patent Rules*, the claim must specify that the liver cell receptors are carbohydrate receptors (see page 14, lines 23-31).

Claim 32 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. Liver endothelial cells are not liver cell receptors and therefore, the inclusion of liver endothelial cells in a Markush group defining liver cell receptors is inappropriate.

In order to improve clarity and syntax, the following clerical errors must be addressed. The iron chelator "diethylenetriamine pentaacetic acid" is misspelled in claims 2, 15, 17, 19, 33 and 36. The chemical formula for chloroform is mistakenly written in claims 14 and 16 with an capital I instead of a lower case L.

In view of the foregoing defects, the applicant is requisitioned, under subsection 30(2) of the *Patent Rules*, to amend the application in order to comply with the *Patent Act* and the *Patent Rules* or to provide arguments as to why the application does comply.

Under section 34 of the *Patent Rules*, any amendment made in response to this requisition must be accompanied by a statement explaining the nature thereof, and how it overcomes each of the above objections.

Should any further prosecution of this application ensue, the applicant is requisitioned to provide particulars, under subsection 29(1) of the *Patent Rules*, of the prior art cited in respect of the United States Patent and Trademark Office, and European Patent Office applications describing the same invention on behalf of the applicant or on behalf of any other person claiming under an inventor named in the present application, and the patent numbers, if granted. Amendment to avoid references cited abroad may expedite the prosecution. In accordance with subsection 29(3) of the *Patent Rules*, if the particulars are not available to the applicant, the reason must be stated.

In order to assist the prosecution of this application, the applicant is requisitioned to provide a copy of all non-patent documents cited during the prosecution by the United States Patent and Trademark Office and European Patent Office applications. under subsection 29(1) of the *Patent Rules*. In accordance with subsection 29(3) of the *Patent Rules*, if at least one of the documents is not available to the applicant, the reason must be stated.

The above requisitioned information must be provided regardless of the current status of the foreign applications.

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